Letter Re: Dynamic pituitary-adrenal interactions in response to Cardiac surgery

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Word Count (Main body): 569

Key words: Glucocorticoid hormones; cortisol, ACTH, Critical illness, Cardiac Surgery, Sampling Frequency, Time-series analysis

No reprints will be ordered

Funding: This work was supported by the British Heart Foundation (BG, GDA), the National Institute for Health Research (NIHR) Bristol Biomedical Research Centre (BG, GDA) and the Engineering and Physical Sciences Research Council (BP, GPN). SLL is supported by the Wellcome Trust.

Conflicts of interest: None declared

The frequency of ‘sampling’ in medicine (hourly vital signs, daily blood tests, annual audits) is usually not based on robust statistical assessment - despite tools being available for the optimal sampling frequency(1). In our study published in Critical Care Medicine(2) we showed that the pulsatility of the Hypothalamic-pituitary-adrenal (HPA) axis still exists during and after cardiac surgery. This pulsatility is generated at a systems level by the positive feedforward and negative feedback of the pituitary and adrenal glands respectively(3) and is essential for end-organ effect(4). We also showed that the sensitivity of the system changes after cardiac surgery, such that the adrenal glands become more sensitive to ACTH. The cortisol profiles of 20 patients having elective coronary artery bypass grafting (CABG) were carried out using 10-minute blood sampling for the 24-hour operative period. In health, the wavelength of each pulse of cortisol and ACTH is approximately an hour(5). After cardiac surgery, the pulse amplitude is larger and the wavelength of each pulse is longer(2). Ten-minute sampling in these patients is both labour intensive and expensive. To inform future studies and clinical practice we conducted a statistical analysis of the data to assess whether less frequent sampling could be undertaken without significant loss of precision. The data contained 10-minute sampling from 20 patients (144 samples per patient). A smoothed common mean for all series was found and the autocorrelation structure of the residuals was estimated by fitting an autoregressive (AR) model of order four to them. Asymptotic forecast variances consistent with the fitted model could then be calculated. The second row of Table 1 contains the square roots of such variances: values which correspond to theoretical root-mean-squared-errors (RMS-Error – analogous to forecast errors) for situations in which data is available at multiples of ten minutes. Relative RMS-Errors are calculated by dividing the RMS-Errors for particular sampling frequencies by those for forecasts based on sampling every ten minutes and also those based only on the residuals' marginal variance.

This analysis shows that halving the sampling rate to every 20 minutes leads to an increase in RMS-Error by a factor of about 1.5. Increasing the sampling interval further leads to corresponding increases in the RMS-Errors. Hourly sampling leads to a RMS-Error of about 2.8 times that of 10-minute sampling (See Table 1). This rises towards an asymptote - at a sampling frequency of 2-hourly, the RMS-Error is at 80% of its maximum value.

One of the strengths of this analysis is that the results are relatively robust to changes in the time-series model for the mean-adjusted cortisol values. For example, autoregressive processes of the order 2, 3, 4, and 5 all lead to very similar results in terms of model fit and corresponding forecast variances. One of the weaknesses

of this technique is that it assumes that the forecast variances and therefore optimal sampling frequency is the same for all patients. However, individual sampling frequencies are unlikely to be useful in clinical practice. This modelling *does* have implications for both clinical practice and future academic study. It shows that frequent (10 minute) sampling is necessary to fully characterise the pulsatile nature of plasma cortisol. The ability of a single value to predict what the cortisol level will be even 2 hours later is so inaccurate as to not be useful and therefore, a single, point cortisol test is inadequate to assess adrenal function in the post-operative cardiac surgical patient (except for a cortisol level of zero - ie absolute deficiency).

Table Legends

Table 1. *Absolute and relative RMSEs for different sampling frequencies of cortisol in patients having elective coronary artery surgery.*

References

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